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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,956	03/15/2004	Akihide Fujimoto	89212.0017	2356

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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
08/06/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	**Application No.** 10/801,956	**Applicant(s)** FUJIMOTO ET AL.	
	Examiner STEVEN C. POHNERT	**Art Unit** 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,12,13,26,27,35,36,44,46,52,53,58,60 and 74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,12,13,26,27,35,36,44,46,52,53,58,60 and 74* is/are rejected.

7)☒ Claim(s) *52 and 53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/20/2009 has been entered.

Formal Matters and Claim status

This action is in response to the claim amendment filed 8/21/2008 and the arguments filed 6/6/2008.

The claims 2-5, 7-11, 14-25, 28-34, 37-43, 45, 47-51, 54-57, 59, 61-73, and 75-96 are canceled.

Claims 1, 6, 12-13, 26-27, 35-36, 44, 46, 52-53, 58, 60, and 74 are pending.

The objection to claims 35-37, 58-61, 87-88 and 91-92 have been withdrawn in view of the amendment.

The 112-2nd paragraph rejections of claims 27-28, 36-37, 46-47, 60-61 and 87-92 has been withdrawn in view of the cancellation of the claims.

The 102 rejection of claim 26 based on Soengas has been withdrawn upon further consideration.

Claim Objections

2. Claims 52 and 53 are objected to because of the following informalities:

Claim 52 is objected to as it recites "RLM" but does not recite the full terminology for the acronym and the acronym may have alternative meanings.

Claim 53 is objected to as it recites "ITM" but does not recite the full terminology for the acronym and the acronym may have alternative meanings.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 6, 12, 13, 26, 27, 74, are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Gocke et al (US Patent 6156504, issued Dec 5, 2000).

This rejection was previously presented but has been modified to reflect the claim amendments and improve clarity.

Soengas et al teaches detection of loss of heterozygosity of 12q22-23 region in 24 patients using 6 12q22-23 microsatellite markers including D12S1657, D12S393, D12S1706, and D12S346 (see figure 1 and legend). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR.

Soengas teaches loss of microsatellite markers (D12S1657, D12S393, D12S1706, and D12S346) in the 12q22-23 regions in patients are detected in metastatic melanoma (see abstract; page 207 2nd column, lines12-14). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR. Soengas teaches LOH of markers D12S1657, D12S393, D12S1706, and D12S346 is associated with loss of APAF1 expression (page 210, 2nd column).

Soengas teaches there is a high rate of APAF-1 LOH in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soengas thus teaches LOH of APAF-1 in melanoma indicates a high probability of metastatic cancer.

Soengas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

Soengas teaches there is correlation of APAF-1 levels and response to Adriamycin in melanoma cells (see page 209, column 1, lines 8-10). Soengas teaches that APAF-1 levels are lower in melanomas with APAF-1 LOH. Soengas thus teaches APAF-1 LOH results in poor efficacy of treatment in melanoma.

Soengas does not teach the use of accellular DNA from plasma, serum, or blood as a sample (1, 6, 12, 13, 26, 27, 74).

However, Gocke et al teaches methods of using of extracellular DNA found serum (2, 7) or plasma (claims 3,8,) for the detection of cancer (see title, abstract). Gocke teaches peripheral blood (claims 81, 82,); plasma or serum is easily accessible and amenable for DNA amplification (see column 2, lines 54-55). Gocke et al further teaches that many studies have used nucleic acid amplification to detect intracellular DNA extracted from circulating cells in blood (see column 2, line 56-60). Gocke teaches use of blood, plasma, or serum allows rapid and timely extraction and sensitive detection of extra cellular tumor associated or extracellular mutated oncogenic DNA (see column 3, lines 60-63).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Soengas method of detecting markers D12S1657, D12S393, D12S1706, and D12S346 by use of peripheral blood, plasma, or serum as taught by Gocke, because Gocke teaches blood, plasma, or serum is easily accessible and amenable for DNA amplification and thus detection of nucleic acids. The ordinary artisan would further be motivated because, Gocke teaches use of plasma or serum allows rapid and timely extraction and sensitive detection of

extracellular tumor associated or extracellular mutated oncogenic DNA. Thus as Gocke teaches methods of nucleic acid analysis by PCR amplification as taught by Soengas the artisan would have a reasonable expectation of success. The combination of Soengas and Gocke would have resulted in a method of detecting the presence or absence of D12S1657, D12S393, D12S1706, and D12S346 markers in accellular DNA from blood, serum, or plasma and from this detection allow the detection of melanoma.

Response to Arguments

The response asserts that claim 26 is not anticipated by the teachings of Soengas as the response asserts that that Soengas compares the expression of APAf-1 in metastatic and primary tumors and further asserts that Soengas "fails to show that expression of APAF-1 necessarily correlates with LOH. These arguments have been thoroughly reviewed bur are not considered persuasive as Soegnas teaches, "Tumors with loss of heterozygosity (LOH) expressed little APAF-1 message "(page 207, 2nd column, last paragraph). Further Soengas teaches metastatic tumors had decreased expression of APAF1, while only one primary tumor had decreased expression of APAF-1 and suggests that loss is APAF-1 is associated with progression of melanoma (page 208, 1st column). Thus Soegnas does suggest that LOH of the markers which are indicative of decreased expression and indicative of disease progression.

The response continues by asserting that disease Soegnas speculated without any evidence that loss of APAF-1 may be associated with disease progression. Soengas teaches metastatic tumors had decreased expression of APAF1, while only one primary tumor had decreased expression of APAF-1 and suggests that loss is

APAF-1 is associated with progression of melanoma (page 208, 1st column), while Soengas teaches LOH of the claimed markers was high in metastatic melanoma (page 207, 2nd column). Thus contrary to the assertion of the response Soegnas has evidence.

The response continues by asserting that Soegnas had incorrectly identified the location of the APAF1 gene and points to the instant specification. This argument has been thoroughly reviewed but is not considered persuasive as the instant claims are not drawn to APAF-1 but the claimed markers. The location of APAF1 is thus beyond the scope of the claimed invention.

The response of asserts that Soengas does not teach detecting molecular markers of accellular DNA from serum or plasma (claim 1) or detecting melanoma from accellular DNA for detection of melanoma (claim 6). The response further asserts that the teachings of Gocke do not overcome these deficiencies. The response asserts that Gocke is cited for the use of serum or plasma for DNA amplification. It is noted that a prior art reference is considered as a whole and for all it stands for. These arguments have been thoroughly reviewed but are not considered persuasive Gocke teaches a method of detecting cancer by use of extracellular DNA and Soengas teaches loss of D12S1657, D12S393, D12S1706, and D12S346 is common in melanoma. Thus the teachings of Soengas and Gocke teach and /or suggest every limitation of the claims thus rendering the instant claims obvious. The combination of Soengas and Gocke is a combination of two known methods for the detection of nucleic acids for the purpose of detecting cancer.

The response further asserts the teachings of Fujiwara suggest that LOH of DNA markers are not necessarily identical or consistent in tumor cells and accellular DNA. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not require comparison to a tumor sample and thus the arguments are beyond the scope of the claimed invention. Further Fujiwara teaches, “We and others have examined molecular markers such as melanoma- associated antigen mRNA markers in RT-PCR assays to detect melanoma cells in blood, lymph nodes, and various other organs (38, 39). These molecular markers have been shown to be very useful in detecting metastatic melanoma cells and disease progression.” (page 1570, 1st column). Fujiwara further teaches, "the assay is very specific in that none of the normal samples tested showed LOH at any loci" (page 1570, 2nd column, 1st full paragraph). Fujiwara further teaches the frequency and number of microsatellite markers with LOH in plasma significantly increased in more advanced clinical stages of the (page 1570, 2nd column, 3rd paragraph). Fujiwara further teaches, “This study illustrates the clinical se or microsatellite analysis in detecting tumor DNA in plasma of melanoma patients. The analysis of LOH in plasma provides a logistically practical assay to monitor genetic changes during melanoma progression. The study demon- strafes that at early clinical stages, release of DNA (LOH marker) is limited. Plasma LOH analysis may be more suitable to monitor stage It to stage IV progression before and during therapy as well as during post treatment 'follow-up. The markers may be also useful to detect subclinical disease recurrence in disease-free patients. Tumor progression is dynamic, and the genetic changes that concurrently occur are also ongoing. The most significant

advantage of this approach in assessing plasma compared with direct analysis of tumor biopsies is the ability to monitor disease progression and genetic changes without assessing the tumor. This is particularly important during early phases of distant disease spread in which subclinical disease is undetectable by conventional imaging techniques. "Thus Fujiwara does not suggest that use LOH of accellular DNA markers is unpredictable, but suggests their use.

4. Claims 35 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Chapman et al (Journal of Clinical Oncology.(1999) volume 17, pages 2745-2751), Healy (oncogene (1998) volume 16, pages 2213-2218) and O'Day et al (Journal of Clinical Oncology (1999) volume 17, pages 2752-2761).

The claims 35 are drawn to loss of heterozygosity being indicative of poor efficacy of biochemotherapy. The specification does not present a definition of "efficacy" or "poor efficacy." Further the specification nor claims set forth what the efficacy is relative to. Thus poor efficacy is being given the broadest reasonable interpretation as survival after treatment.

The claim 58 is drawn to loss of heterozygosity being indicative of low probability of responsiveness to biochemotherapy. The specification does not present a definition of "low probability of responsiveness." Thus of low probability of responsiveness is being given the broadest reasonable interpretation as survival after treatment.

With regards to claims 35, Soengas teaches there is correlation of APAF-1 levels and response to adriamycin in melanoma cells (see page 209, column 1, lines 8-10).

Soengas teaches that APAF-1 levels are lower in melanomas due to APAF-1 LOH. Soengas teaches detection of LOH for APAF-1 by assaying markers D12S1657, D12S393, D12S1706, and D12S346 (see figure 1B). Soengas thus teaches D12S1657, D12S393, D12S1706, and D12S346 LOH results in poor efficacy of treatment in melanoma.

With regards to claim 58, Soengas teaches assessment of teaches D12S1657, D12S393, D12S1706, and D12S346 status improves therapeutic management for patients, as it is a required for apoptosis and thus a marker of chemosensitivity (see page 210, 2nd column, lines 20-26).

Soengas does not teach that loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 is predictive of response to biochemotherapy or predicted efficacy of response to biochemotherapy. Soengas does not teach melanoma biochemotherapy comprising dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2 and tamoxifen.

However, Soengas teaches "Assessment of Apaf-1status may therefore improve the therapeutic management of patients with malignant melanoma" (see page 210, 2nd column last line of text).

Chapman teaches, " patients with stage IV melanoma, based on American Joint Committee on Cancer (AJCC) criteria, have a universally poor prognosis with a median survival time of 3 to 11 months, depending on subgroup analyzed" (page 2745, 1st column). Chapman teaches, “Although initial response rates have often been encouraging in single-institution trials (typically 40% to 50%), subsequent phase II trials

have not confirmed these response rates,9-14 and prospective phase III trials failed to demonstrate a superiority of many of these regimens over dacarbazine alone" (page 2745, 1st column). Chapman further teaches, "Patients with metastases confined to soft tissue sites (skin, lymph nodes, or lung) are more likely to respond to chemotherapy and, in many databases, have a better prognosis than patients with metastases to other sites. Of the 226 patients assessable for tumor response, 99 (44%) had metastasis confined to soft tissue sites. In this group of patients, the response rate to the Dartmouth regimen was higher than the response rate to dacarbazine (32% v 14%), with the difference reaching statistical significance. Despite a higher rate of tumor responses in patients with soft tissue metastases treated on the Dartmouth arm, there was no improvement in overall survival. This is not surprising given that, in both treatment arms, the response rates were relatively low and there were no complete responses. The European Organization for Research and Treatment of Cancer Melanoma Cooperative Group has reported a similar observation in which interleukin-2–based treatments doubled the response rate but had no apparent impact on survival.31 Other subsets of patients were analyzed (women and patients with visceral metastases), but no increase in response rate or survival was observed for the Dartmouth arm" (page 2750, 1st column). Thus Chapman teaches that subjects with stage IV melanoma have a poor response to treatment, poor survival time, and thus poor efficacy of response to treatment, although those with soft tissue metastasis were more likely to respond to treatment.

Healy teaches, "Some (but not all) studies on DNA ploidy in melanoma have suggested that individuals with tumours exhibiting aneuploidy have a poorer outcome" (page 2213, 2nd column, last paragraph). Healy further teaches, "metastatic melanoma is a late stage of disease, and nearly all patients with metastases will eventually die from their melanoma" (page 2213, 2nd column, last paragraph). Healy further teaches, "However, based on the FAL scores, the results suggest that the overall level of genomic instability (as well as losses of 6q and 10q) may determine the clinical behavior of the melanoma and the ultimate clinical survival. This association of higher FAL scores with a poorer clinical, outcome, independent of the depth of invasion, suggests that this variable might allow the identification both of individuals with thin melanomas who will eventually die from their tumor and of subjects with paradoxically thick melanomas in whom the melanoma will not metastasize." (page 2215, 2nd column, last paragraph).

Further O'Day et al teaches "5-day modified concurrent biochemotherapy regimen of dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alpha-2b, and tamoxifen was repeated at 21-day intervals" (see abstract). O'Day teaches pretreatment evaluation (page 2753, 2nd column). O'Day further teaches, "the concurrent biochemotherapy regime of Legha et al was modified in an effort to reduce toxicity further while maintaining or improving efficacy. These modifications consisted of decrescendo IL-2 dosing, routine use of growth factor support with granulocyte colony-stimulating factor (G-CSF), and low-dose tamoxifen. The total IL-2 dose was unchanged, but this agent was administered in a decrescendo schedule, with a

higher initial dose in the first 24 hours that decreased progressively on subsequent days. This change in IL-2 dosing is based on preclinical and clinical studies suggesting that decrescendo dosing improves efficacy and reduces cumulative IL-2 toxicity.29, 30 Routine post treatment G-CSF was implemented because of the high incidence of grade myelosuppression, fever/neutropenia, and infection in Legha's concurrent biochemotherapy trial. Tamoxifen was added to the regimen because at the time the study was designed, data suggested potential synergistic effects with chemotherapy" (page 27531st column, 2nd full paragraph).

Therefore, it would be prima facie obvious to one of skill in the art at the time the invention was made to predict long term survival (efficacy of response) of stage IV melanoma to treatment with dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen in patients or the probability of responsiveness to dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen in view of the teachings of Soengas, Champman, Healy and O'Day with a reasonable expectation of success. Chapman and Healy teach that subjects with stage IV melanomas and metastasis had poor longer term prognosis and thus poor response to biochemotherapy. Chapman teaches only 5% to 20% of subjects with stage IV melanoma responded to biochemotherapy, while Healy teaches genomic instability plays a large role in clinical outcome. The teachings of Soengas suggest that loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 markers results decreased apoptosis, which in turn results in increased chemoresistance to chemotherapeutic agents in melanoma. Thus, it would have been obvious to one of

skill in the art that subjects with stage IV melanoma and LOH of markers known to be associated with decreased apoptosis in melanoma in response to treatment with chemotherapeutic drugs as Chapman and O'Day teach they have poor survival and thus poor prognosis. It would have been obvious to one of skill in the art in view of the teachings of Soengas and O'Day to use D12S1657, D12S393, D12S1706, and D12S346 to predict responsiveness or efficacy of treatment as Soengas teaches "Assessment of Apaf-1status may therefore improve the therapeutic management of patients with malignant melanoma" (see page 210, 2nd column last line of text). The artisan would be motivated because Soengas suggest such a method as cited above. The artisan would have a reasonable expectation of success as the artisan would merely be using an assay to predict the response to a known biochemotherapy.

Response to arguments

The response reiterates the arguments addressed above with respect to Soengas.

The response continues by asserting in vitro experiments do not necessarily reflect in vivo experiments and presents the teachings of Walter and Miller as evidence. These arguments have been thoroughly reviewed but are not considered persuasive as the instant rejection has provided the teachings of Healy and Chapman to demonstrate that Stage IV melanoma has a poor response to biochemotherapy as indicated by long term survival in vivo. Thus the rejection is not merely relying of the in vitro studies of Soengas, but the in vivo studies of Healy and Chapman, which are specific to melanoma as opposed to the general teachings of Walter and Miller. It is further noted

the specification teachings with respect to response to biochemotherapy are limited to 49 subjects and have not been replicated. Thus as Chapman teaches, "Although initial response rates have often been encouraging in single-institution trials (typically 40% to 50%), subsequent phase II trials have not confirmed these response rates,9-14 and prospective phase III trials failed to demonstrate a superiority of many of these regimens over dacarbazine alone" (page 2745, 1st column). The combination of Soengas, Chapman, Healy, and O'Day is at least as predictable as the teachings of the instant specification.

The response continues by noting that O'Day does not overcome the deficiencies of Soengas. These arguments have been addressed in the rejection by the inclusion of the teachings of Chapman and Healy.

5. Claims 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Taback et al (Cancer Research (2001) volume 61, pages 5723-5726) and Chapman et al (Journal of Clinical Oncology.(1999) volume 17, pages 2745-2751).

Soengas et al teaches detection of loss of heterozygosity of 12q22-23 region in 24 patients using 6 12q22-23 microsatellite markers including D12S1657, D12S393, D12S1706, and D12S346 (see figure 1 and legend). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR.

Soengas teaches loss of APAF1 and microsatellite markers (D12S1657, D12S393, D12S1706, and D12S346) in the 12q22-23 regions in patients are detected in

metastatic melanoma (see abstract; page 207 2nd column, lines12-14). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR. Soengas teaches there is a high rate of APAF-1 LOH (including D12S1657, D12S393, D12S1706, and D12S346) in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soengas thus teaches LOH of APAF-1 (including D12S1657, D12S393, D12S1706, and D12S346) in melanoma indicates a high probability of metastatic cancer.

Soengas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

Soengas conclude by stating that, "our results imply the APAF-1 loss contributes to the aggressive nature and extreme chemoresistance of metastatic melanoma" page 210 2nd column, and last paragraph).

Soengas thus teaches a method of detecting melanoma by loss of heterozygosity for DNA markers D12S1657, D12S393, D12S1706, and D12S346, indicates progression of melanoma.

Soengas does not teach providing samples with stage III or Stage IV melanoma.

However, Taback teaches loss of heterozygosity of microsatelite markers in stage III and stage IV melanoma is associated with a decreased probability of survival (figure 1). Taback teaches, "The findings of additional LOH in more advanced tumors (i.e., highly invasive primary lesions and advanced metastasis) suggests that these additional events, not always present in early stages of primary tumors, may be associated with, or representative of, more aggressive tumors that may be of prognostic

value" (page 5723, 2nd column, 1st paragraph). Taback further teaches that once melanoma has metastasized, overall prognosis is generally poor (page 5725, 1st column, 1st full paragraph).

Chapman teaches, " patients with stage IV melanoma, based on American Joint Committee on Cancer (AJCC) criteria, have a universally poor prognosis with a median survival time of 3 to 11 months, depending on subgroup analyzed" (page 2745, 1st column). Chapman further teaches, "Patients with metastases confined to soft tissue sites (skin, lymph nodes, or lung) are more likely to respond to chemotherapy and, in many databases, have a better prognosis than patients with metastases to other sites. Of the 226 patients assessable for tumor response, 99 (44%) had metastasis confined to soft tissue sites. In this group of patients, the response rate to the Dartmouth regimen was higher than the response rate to dacarbazine (32% v 14%), with the difference reaching statistical significance. Despite a higher rate of tumor responses in patients with soft tissue metastases treated on the Dartmouth arm, there was no improvement in overall survival. This is not surprising given that, in both treatment arms, the response rates were relatively low and there were no complete responses. The European Organization for Research and Treatment of Cancer Melanoma Cooperative Group has reported a similar observation in which interleukin-2–based treatments doubled the response rate but had no apparent impact on survival.31
Other subsets of patients were analyzed (women and patients with visceral metastases), but no increase in response rate or survival was observed for the Dartmouth arm" (page 2750, 1st column). Thus Chapman teaches that subjects with

stage IV melanoma have a poor response to treatment, poor survival time, and thus poor efficacy of response to treatment, although those with soft tissue metastasis were more likely to respond to treatment.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to analyze stage III or stage IV melanoma as taught by Taback and Chapman in the method of Soengas. The artisan would be use stage III or stage IV melanoma samples in the method of Soengas as there are only four stages of melanoma known and thus a limited number of possibilities. The artisan would have a reasonable expectation of success of determining a low probability of survival of patients with LOH of stage III or stage IV melanoma have a poor prognostic outcome and further because Chapman teaches subjects with Stage IV have poor prognosis and survival, while Soengas teaches LOH of D12S1657, D12S393, D12S1706, and D12S346 is associated with decreased apoptosis in response to chemotherapy and thus poor outcome.

Response to Arguments

The response reiterates the arguments previously presented with respect to Soegnas. These arguments have been previously addressed.

The response asserts that Taback does not teach the claimed markers. This argument has been thoroughly reviewed but is not considered persuasive as Soengas is being relied upon for the teaching of the markers. Further the newly presented reference of Chapman teaches that subjects with stage IV melanoma have a poor chance of survival.

6. Claims 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) and of Taback et al (Cancer Research (2001) volume 61, pages 5723-5726) and Chapman et al (Journal of Clinical Oncology.(1999) volume 17, pages 2745-2751) as applied to claim 44 and 45 above, and further in view of Yu et al (Cancer (1999) volume 86, pages 612-627).

The teachings of Soengas, Taback, and Chapman are set forth above.

Soengas, Taback, and Chapman do not teach melanoma being regional lymph node metastasis (RLM) or in transit metastasis (ITM).

However, Yu teaches early detection of AJCC stage III metastasis's to regional lymph nodes (RLM) (page 625, 2nd column 1st paragraph). Yu further teaches melanoma metastasis in transit were known (page 620, 1st column, 1st full paragraph).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to analyze IRM or ITM melanoma as taught by Yu in the method of Soengas, Taback, and Chapman. The artisan would be use IRM or ITM melanoma samples in the method of Soengas, Taback, and Chapman as there are known forms of melanoma mestasis. The artisan would have a reasonable expectation of success of determining a low probability of survival of patients with metastatic melanoma including IRM and ITM because Soengas teaches LOH of D12S1657, D12S393, D12S1706, and D12S346 is associated with decreased apoptosis in response to chemotherapy and thus poor outcome.

Response to Arguments

The response asserts that claim 44 is not obvious over the teachings of Soegnas and Taback. This argument has been addressed previously. As the response provides no arguments to the instant combination the rejection is maintained.

7. Claims 1, 6, 12, 13, 26, 27, 74, are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Fujiwara et al (Cancer Research (1999) volume 59, pages 1567-1571).

Soengas et al teaches detection of loss of heterozygosity of 12q22-23 region in 24 patients using 6 12q22-23 microsatellite markers including D12S1657, D12S393, D12S1706, and D12S346 (see figure 1 and legend). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR.

Soengas teaches loss of microsatellite markers (D12S1657, D12S393, D12S1706, and D12S346) in the 12q22-23 regions in patients are detected in metastatic melanoma (see abstract; page 207 2nd column, lines12-14). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR. Soengas teaches LOH of markers D12S1657, D12S393, D12S1706, and D12S346 is associated with loss of APAF1 expression (page 210, 2nd column).

Soengas teaches there is a high rate of APAF-1 LOH in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soengas thus teaches LOH of APAF-1 in melanoma indicates a high probability of metastatic cancer.

Soengas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

Soengas teaches there is correlation of APAF-1 levels and response to Adriamycin in melanoma cells (see page 209, column 1, lines 8-10). Soengas teaches that APAF-1 levels are lower in melanomas with APAF-1 LOH. Soengas thus teaches APAF-1 LOH results in poor efficacy of treatment in melanoma.

Soengas does not teach the use of accellular DNA from plasma, serum, or blood as a sample (1, 6, 12, 13, 26, 27, 74).

However, Fujiwara teaches naked DNA released from tumor cells is released, enriched and remains stable in the blood of cancer patients and used for detecting cancer specific DNA markers (1567, 1st column, bottom). Fujiwara teaches genetic changes resulting progression of melanoma from stage II to stage IV are not well understood (1567, 2nd column, 2nd full paragraph). Fujiwara teaches multiple LOH markers can be detected in the plasma of melanoma patients, but not healthy donors (1567, 2nd column, 2nd full paragraph). Fujiwara teaches, "The study also demonstrated that melanomas release tumor specific genetic markers in the blood that correlated to the patients respective melanoma legion" (1567, 2nd column, last paragraph). Fujiwara further teaches the frequency and number of microsatellite markers with LOH in plasma significantly increased in more advanced clinical stages of the (page 1570, 2nd column, 3rd paragraph). Fujiwara further teaches, "This study illustrates the clinical se or microsatellite analysis in detecting tumor DNA in plasma of melanoma patients. The analysis of LOH in plasma provides a logistically practical assay to monitor genetic

changes during melanoma progression. The study demonstrates that at early clinical stages, release of DNA (LOH marker) is limited. Plasma LOH analysis may be more suitable to monitor stage II to stage IV progression before and during therapy as well as during post treatment 'follow-up. The markers may be also useful to detect subclinical disease recurrence in disease-free patients. Tumor progression is dynamic, and the genetic changes that concurrently occur are also ongoing. The most significant advantage of this approach in assessing plasma compared with direct analysis of tumor biopsies is the ability to monitor disease progression and genetic changes without assessing the tumor. This is particularly important during early phases of distant disease spread in which subclinical disease is undetectable by conventional imaging techniques. " Thus Fujiwara does not suggest that use LOH of accellular DNA markers is unpredictable, but suggests their use. Further Fujiwara teaches, " We and others have examined molecular markers such as melanoma- associated antigen mRNA markers in RT-PCR assays to detect melanoma cells in blood, lymph nodes, and various other organs (38, 39). These molecular markers have been shown to be very useful in detecting metastatic melanoma cells and disease progression." Page (1570, 1st column)

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Soengas method of detecting markers D12S1657, D12S393, D12S1706, and D12S346 by use of peripheral blood, plasma, or serum as taught by Fujiwara, because Fujiwara teaches blood, plasma, or serum is easily accessible and amenable for DNA amplification and thus detection of

nucleic acids. The ordinary artisan would further be motivated because, Fujiwara teaches, "The most significant advantage of this approach in assessing plasma compared with direct analysis of tumor biopsies is the ability to monitor disease progression and genetic changes without assessing the tumor. This is particularly important during early phases of distant disease spread in which subclinical disease is undetectable by conventional imaging techniques." Thus as Fujiwara teaches methods of nucleic acid analysis by PCR amplification as taught by Soengas the artisan would have a reasonable expectation of success. The combination of Soengas and Fujiwara would have resulted in a method of detecting the presence or absence of D12S1657, D12S393, D12S1706, and D12S346 markers in accellular DNA from blood, serum, or plasma and from this detection allow the detection of melanoma.

Response to Arguments

This is a new ground of rejection. The arguments directed to Soengas have been previously addressed.

8. Claims 35-36, 58, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Fujiwara et al (Cancer Research (1999) volume 59, pages 1567-1571) as applied to claim1, 6, 12, 13, 26, 27, 74, above, and further in view of Chapman et al (Journal of Clinical Oncology.(1999) volume 17, pages 2745-2751), Healy (oncogene (1998) volume 16, pages 2213-2218) and O'Day et al (Journal of Clinical Oncology (1999) volume 17, pages 2752-2761).

The claims 35-36 are drawn to loss of heterozygosity being indicative of poor efficacy of biochemotherapy. The specification does not present a definition of “efficacy” or “poor efficacy.” Further the specification nor claims set forth what the efficacy is relative to. Thus poor efficacy is being given the broadest reasonable interpretation as survival after treatment.

The claims 58 and 60 are drawn to loss of heterozygosity being indicative of low probability of responsiveness to biochemotherapy. The specification does not present a definition of “low probability of responsiveness.” Thus of low probability of responsiveness is being given the broadest reasonable interpretation as survival after treatment.

The teachings of Fujiwara and Soegnas are set forth above.

Soengas and Fujiwara do not teach that loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 is predictive of response to biochemotherapy or predicted efficacy of response to biochemotherapy. Soengas and Fujiwara do not teach melanoma biochemotherapy comprising dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2 and tamoxifen.

However, Soengas teaches "Assessment of Apaf-1status may therefore improve the therapeutic management of patients with malignant melanoma" (see page 210, 2nd column last line of text).

Chapman teaches, " patients with stage IV melanoma, based on American Joint Committee on Cancer (AJCC) criteria, have a universally poor prognosis with a median survival time of 3 to 11 months, depending on subgroup analyzed” (page 2745, 1st

column). Chapman teaches, "Although initial response rates have often been encouraging in single-institution trials (typically 40% to 50%), subsequent phase II trials have not confirmed these response rates,9-14 and prospective phase III trials failed to demonstrate a superiority of many of these regimens over dacarbazine alone" (page 2745, 1st column). Chapman further teaches, "Patients with metastases confined to soft tissue sites (skin, lymph nodes, or lung) are more likely to respond to chemotherapy and, in many databases, have a better prognosis than patients with metastases to other sites. Of the 226 patients assessable for tumor response, 99 (44%) had metastasis confined to soft tissue sites. In this group of patients, the response rate to the Dartmouth regimen was higher than the response rate to dacarbazine (32% v 14%), with the difference reaching statistical significance. Despite a higher rate of tumor responses in patients with soft tissue metastases treated on the Dartmouth arm, there was no improvement in overall survival. This is not surprising given that, in both treatment arms, the response rates were relatively low and there were no complete responses. The European Organization for Research and Treatment of Cancer Melanoma Cooperative Group has reported a similar observation in which interleukin-2–based treatments doubled the response rate but had no apparent impact on survival.31 Other subsets of patients were analyzed (women and patients with visceral metastases), but no increase in response rate or survival was observed for the Dartmouth arm" (page 2750, 1st column). Thus Chapman teaches that subjects with stage IV melanoma have a poor response to treatment, poor survival time, and thus

poor efficacy of response to treatment, although those with soft tissue metastasis were more likely to respond to treatment.

Healy teaches, “Some (but not all) studies on DNA ploidy in melanoma have suggested that individuals with tumours exhibiting aneuploidy have a poorer out-come” (page 2213, 2nd column, last paragraph). Healy further teaches, “metastatic melanoma is a late stage of disease, and nearly all patients with metastases will eventually die from their melanoma” (page 2213, 2nd column, last paragraph). Healy further teaches, “However, based on the FAL scores, the results suggest that the overall level of genomic instability (as well as losses of 6q and 10q) may determine the clinical behavior of the melanoma and the ultimate clinical survival. This association of higher FAL scores with a poorer clinical, outcome, independent of the depth of invasion, suggests that this variable might allow the identification both of individuals with thin melanomas who will eventually die from their tumour and of subjects with paradoxically thick melanomas in whom the melanoma will not metastasize.” (page 2215, 2nd column, last paragraph).

Further O’Day et al teaches “5-day modified concurrent biochemotherapy regimen of dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alpha-2b, and tamoxifen was repeated at 21-day intervals” (see abstract). O’Day teaches pretreatment evaluation (page 2753, 2nd column). O’Day further teaches, “the concurrent biochemotherapy regime of Legha et al was modified in an effort to reduce toxicity further while maintaining or improving efficacy. These modifications consisted of decrescendo IL-2 dosing, routine use of growth factor support with granulocyte colony-

stimulating factor (G-CSF), and low-dose tamoxifen. The total IL-2 dose was unchanged, but this agent was administered in a decrescendo schedule, with a higher initial dose in the first 24 hours that decreased progressively on subsequent days. This change in IL-2 dosing is based on preclinical and clinical studies suggesting that decrescendo dosing improves efficacy and reduces cumulative IL-2 toxicity.29, 30 Routine post treatment G-CSF was implemented because of the high incidence of grade myelosuppression, fever/neutropenia, and infection in Legha's concurrent biochemotherapy trial. Tamoxifen was added to the regimen because at the time the study was designed, data suggested potential synergistic effects with chemotherapy" (page 27531st column, 2nd full paragraph).

Therefore, it would be prima facie obvious to one of skill in the art at the time the invention was made to predict long term survival (efficacy of response) of stage IV melanoma to dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen in patients or the probability of responsiveness to dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen in view of the teachings of Soengas and Fujiwara with a reasonable expectation of success. Chapman and Healy teach that subjects with stage IV melanomas and metastasis had poor longer term prognosis and thus poor response to biochemotherapy. Chapman teaches only 5% to 20% of subjects with stage IV melanoma responded to biochemotherapy, while Healy teaches genomic instability plays a large role in clinical outcome. The teachings of Soengas suggest that loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 markers results decreased apoptosis, which in turn

results in increased chemoresistance to chemotherapeutic agents in melanoma. Thus, it would have been obvious to one of skill in the art that subjects with stage IV melanoma and LOH of markers known to be associated with decreased apoptosis in melanoma in response to treatment a chemotherapeutic drug (adriamycin) would also be associated with decreased apoptosis and thus chemoresistance to other known chemotherapeutic agents (dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen). It would have been obvious to one of skill in the art in view of the teachings of Soengas and O'Day to use D12S1657, D12S393, D12S1706, and D12S346 to predict responsiveness or efficacy of treatment as Soengas teaches "Assessment of Apaf-1status may therefore improve the therapeutic management of patients with malignant melanoma" (see page 210, 2nd column last line of text). The artisan would be motivated because Soengas and Fujiwara suggest such a method as cited above. The artisan would have a reasonable expectation of success as the artisan would merely be using an assay to predict the response to a known biochemotherapy.

Response to Arguments

This is a new ground of rejection. The arguments directed to Soengas have been previously addressed.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C. POHNERT whose telephone number is

(571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Steven C Pohnert/
Examiner, Art Unit 1634

Steven Pohnert